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(54) **METHODS AND COMPOSITIONS RELATED TO WRAPPING OF DEHYDRONS**

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See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,623,486	A	11/1986	Lombardino	514/217.05
5,399,363	A	3/1995	Liversidge et al.	424/490
5,459,127	A *	10/1995	Felgner et al.	424/450
5,521,184	A	5/1996	Zimmermann	514/252
5,543,158	A	8/1996	Gref et al.	424/501
5,580,579	A	12/1996	Ruddy et al.	424/489
5,641,515	A	6/1997	Ramtoola	424/489
5,792,451	A	8/1998	Sarubbi et al.	424/85.4
5,885,613	A	3/1999	Holland et al.	424/450
6,114,333	A	9/2000	Davis et al.	514/252.18
6,710,048	B2	3/2004	Kuo et al.	514/252.11
6,894,051	B1	5/2005	Zimmermann et al.	514/252.18
7,910,586	B2 *	3/2011	Netzer et al.	514/247
2004/0248918	A1	12/2004	Kim et al.	514/275
2010/0249122	A1 *	9/2010	Kalman	514/230.5

FOREIGN PATENT DOCUMENTS

WO	WO 03/027100	4/2003
WO	WO 2004/108699	12/2004
WO	WO 2006/108405	10/2006
WO	WO 2006/133046	12/2006

OTHER PUBLICATIONS

Morissette et al. Advanced Drug Delivery Reviews 2004, 56, 275-300.*
Vippagunta et al., abstract, Vippagunta, Sudha R. "Crystalline Solids." Advanced Drug Delivery Reviews 48(2001): 3-26.*
Grant & Hackh's Chemical Dictionary (5th ed. 1987) (p. 542).*
Byrn et al., Solid-State Chemistry of Drugs (2nd Ed. 1999) (pp. 233-247, 234).*
Golub et al. Science (1999), vol. 286 531-537.*
Lala et al. Cancer and Metastasis Reviews (1998), 17(1), 91-106.*
Béni et al., "Molecular interactions in imatinib-DPPC liposomes," *European Journal of Pharmaceutical Sciences*, 27:205-211, 2006.
Capdeville et al., "Glivec (STI571, imatinib), a rationally developed targeted anticancer drug," *Nature Reviews Drug Discovery*, 1:493-502, 2002.
Chen et al., "Molecular basis for specificity in the druggable kinome: sequence-based analysis," *Bioinformatics*, 23:563-572, 2007.
Crespo and Fernández, "Kinase packing defects as drug targets," *Drug Discovery Today*, 12:917-923, 2007.
Deremble and Lavery, "Macromolecular recognition," *Curr. Opin. Struc. Biol.*, 15:171-75, 2005.
Donato and Talpaz, "Clinical use of tyrosine kinase inhibitors: therapy for chronic myelogenous leukemia and other cancers," *Clin. Cancer Res.*, 6:2965-66, 2000.
Fabian et al., "A small molecule-kinase interaction map for clinical kinase inhibitors," *Nature Biotechnology*, 23:329-336, 2005.
Faderl et al., "The biology of chronic myeloid leukemia," *N. Engl. J. Med.*, 341:164-172, 1999.
Fernández and Berry, "Molecular dimension explored in evolution to promote proteomic complexity," *Proc. Natl. Acad. Sci.* USA, 101:13460-13465, 2004.
Fernández and Scheraga, "Insufficiently dehydrated hydrogen bonds as determinants of protein interactions," *Proc. Natl. Acad. Sci. USA*, 100:113-118, 2003.
Fernández and Scott, "Adherence of packing defects in soluble proteins," *Phys. Rev. Lett.*, 91:018102, 2003.
Fernández and Scott, "Dehydron: a structurally encoded signal for protein interaction," *Biophys. J.*, 85:1914-1928, 2003.
Fernández et al., "An anticancer C-kit kinase inhibitor is re-engineered to make it more active and less cardiotoxic," *J. Clin. Invest.*, 117:4044-4054, 2007.
Fernández et al., "Inhibitor design by wrapping packing defects in HIV-1 proteins," *Proc. Natl. Acad. Sci. USA*, 101:11640-11645, 2004.
Fernández et al., "Packing defects as selectivity switches for drug-based protein inhibitors," *PNAS*, 103:323-328, 2006.
Fernández et al., "Rational drug redesign to overcome drug resistance in cancer therapy: imatinib moving target," *Cancer Research*, 67:4028-4033, 2007.

(Continued)

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(57) **ABSTRACT**

This application describes a novel technology in drug discovery and drug-based imaging/detection: the wrapping technology. This technology is based on identified singularities in the structure of soluble proteins. In contrast with drug-design approaches based on standard structural considerations, the packing of a protein, or more precisely, its dehydron pattern, may be used as a selectivity filter to design small-molecule inhibitors. The wrapping technology described herein is a novel form of rational drug design for avoiding side effects in drug therapy and sharpening the inhibitory impact of drugs on the oncokinome.

20 Claims, 16 Drawing Sheets